COALITION FOR BLOOD SAFETY

American Association of Blood Banks - America's Blood Centers -
American Blood Resources Association

September 9, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99N-0193: Supplements and Other Changes to an Approved Application

To Whom It May Concern:

The Coalition for Blood Safety (CFBS), formerly known as the Coalition for Regulatory Reform (CFRR), appreciates the opportunity to submit written comments on the Food and Drug Administration's (FDA) proposed rule, Supplements and Other Changes to an Approved Application. CFBS is composed of the American Association of Blood Banks (AABB), including the American Red Cross (ARC) and the Armed Services Blood Program, America's Blood Centers (ABC), and the American Blood Resources Association (ABRA). CFBS was formed in 1994 after the Food and Drug Administration (FDA) invited the blood banking industry to develop and explore ideas with FDA for a more efficient regulatory system for blood and plasma products. The coalition represents the entire spectrum of blood and plasma collection and transfusion interests.

General Comments

As we have stated in the past, CFBS supports FDA attempts to harmonize the regulations for the drug and biologic industries. CFBS also supports the efforts to decrease the reporting burden for industry. However, the intent of the proposed rule, to help reduce the number of manufacturing changes specifically identified as requiring supplements, is not being realized in the blood banking industry. Instead of decreasing the reporting burden for the blood industry, the Modernization Act has increased the burden. For example, blood establishments are now required to file an annual report, and many of the changes required to be reported in an annual report were never previously reported.

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This proposed rule, and the July 24, 1997 rule *Changes to an Approved Application*; Docket No 95-N-0329 with its corresponding guidance document, *Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Bilogoical Products and Biological Products,* provide examples of manufacturing changes that are not relevant to the blood industry. CFBS has asked for, and were assured after the September 24, 1997 open public meeting on Biologics Regulations: Reporting Changes to an Approved Application, that a guidance specific to the blood industry would be issued. We have yet to see even a draft of this guidance. The blood industry continues to make its best attempt to submit changes in what it feels are the appropriate categories without any clear guidance from FDA. Currently, CBER reviewers have stated that almost all submissions are considered prior approval supplements unless they are specifically identified in the guidance as being in another category. Blood banks continue to submit supplements and the newly required annual reports, which are an increase in our reporting burden, without clear guidance on what is acceptable or what should be submitted. **We reiterate our request that FDA issue guidance that includes examples appropriate to the blood banking industry, and specifically includes information pertaining to the annual report.**

Because there are no changes proposed, the Comparability Protocol is not discussed in this proposed rule. However, CFBS remains perplexed and uninformed about the use of a Comparability Protocol in the blood banking industry. **We request that guidance explaining FDA's intent regarding the Comparability Protocol be issued.**

Specific Comments

Background

In the *Federal Register* of June 28, 1999, the FDA proposed to amend its regulations on supplements and other changes to an approved application to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act.) FDA requested written comments on the proposed rule by September 13, 1999.

The proposed rule would require manufacturers to validate the effect of any manufacturing change on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. The proposed rule also sets forth requirements for changes requiring supplement submission and approval prior to the distribution of the product made using the change, changes requiring supplement submission at least 30 days prior to the distribution of the product, changes requiring supplement submission at the time of distribution, and changes to be described in an annual report.

Although the current Section 601.12 (21 CFR 601.12) for licensed biological products is in full compliance with the new provisions in the Modernization Act, FDA is making the proposed changes in order to maintain harmonization with proposed Section 314.70 for human drug applications.

Discussion

SECTION 600.3 DEFINITIONS

The CFBS appreciates the FDA's continued efforts to harmonize the drug and biologic regulations and to decrease the regulatory burden for reporting manufacturing changes for licensed biological products. While we applaud the agency's actions in this regard, the proposed rule may perpetuate some existing confusion about the applicability of the regulations set forth in part 600 of the CFR. The current CFR part 600 does not include the term drug; however, in the definitions section of proposed section 600.3, as well as in several other places in the proposed rule, the term "drug" is used rather than biological product. This inconsistent terminology could cause confusion. **We request that FDA revise the proposed rule to clarify those sections that apply exclusively to biological products, and those that apply to both drugs and biological products.**

The proposed rule also may cause confusion with respect to the definition of "validate the effects of the change." Under the proposed rule, this phrase means:

> To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors related to the safety or effectiveness of the drug.

Proposed 21 CFR §600.3(ii). However, the agency has narrowly defined the term "validate" in other contexts such as 21 CFR §820.3 and in the guideline on general principles of validation. To avoid confusion, **we request that the agency carefully consider how it has defined these concepts in the past and, to the extent possible, reconcile any definitional differences.**

SECTION 601.12(a)(3)

CFBS has discussed with CBER the reporting burdens associated with Changes to Approved Applications many times in the past. In this new section FDA is proposing that an applicant shall make a manufacturing change submission in accordance with a guideline notice or regulation published in the *Federal Register* that provides for a less burdensome notification of the change. This exception may be used as pharmaceutical science evolves for changes that FDA no longer considers having a substantial potential to have an adverse effect on the product. If this added section will be applied to the blood industry, this would be a welcome addition. However, CBER has indicated that the majority of changes to applications that are submitted by

the blood industry are considered by CBER to have a substantial potential to have an adverse effect on blood products, even when the changes are due to equipment upgrades that have already received 510(k) clearance. **We request that this approach be reconsidered by CBER in order to permit the blood bank industry to realize the benefits of this rule.**

SECTION 601.12(a)(5)

This new section will require that a supplement or annual report include in the cover letter a list of all changes contained in the supplement or annual report. This new requirement will increase the reporting burden for blood establishments. CBER has stated that the new Blood License Application Form, Form FDA 356h, is in and of itself, a cover letter. Why then must blood establishments fill out this additional new "cover letter" and then include all of the information in this "cover letter" in yet another cover letter? Additionally, to require blood establishments to reiterate all of the changes that they have compiled and reported in their annual reports in a cover letter accompanying that annual report is duplication of effort. The annual report itself is an increase in the reporting burden of blood establishments and was not required before the implementation of the BLA with its intended paperwork reduction and regulatory efficiency goals. **We request that multiple cover letters and the requirement to reiterate all of the changes contained in the report be deleted.**

SECTION 601.12(b)(4)

This section which will allow an applicant to request an expedited review of a supplement if a delay in making the change would impose an extraordinary hardship or for public health reasons is new to the biologics regulations. We understand that these requests should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan, that each request will be reviewed on a case-by-case basis and that not all requests may be granted. However, this is a welcome addition and one that may provide some relief to a blood establishment in time of emergency.

SECTION 601.12(c)(2)(i)

This section of the CFR, which the current proposed rule intends to delete, addresses changes in the site of testing from one facility to another as a change that must be filed in a supplement submitted at least 30 days prior to distribution. FDA plans to provide recommendations on the filing mechanism for this change in future guidance documents. This change is of some concern to blood establishments because the alternative filing mechanism has not been discussed prior to deleting this section of the CFR. At times, blood establishments must rapidly change the site of testing from one facility to another and this change must be approved in a short amount of time. In considering alternative reporting mechanisms, the agency should adhere to the "least burdensome" principle in order to ensure the uninterrupted availability of blood and blood products when such changes in testing laboratories are necessary. **CFBS requests that the**

agency provide additional opportunities for public comment before new procedures for reporting such changes are published.

SECTION 601.12(c)(6)

The provision FDA is proposing for this new section of the regulations states that if FDA disapproves a supplemental application, the agency may order the manufacturer to cease distribution of the drug products made utilizing the manufacturing change. The intent of this section is not new to the blood industry. Although CBER has stated in the past that all items in this submission category are of such low risk that they do not expect any problems with the supplement review, they have indicated that there is the possibility of recall if the supplement is not approved. It continues to be the responsibility of the manufacturer to decide whether they wish to take a chance on FDA's decision making process when making this type of change request. Many blood establishments will not even attempt to utilize this provision because of the possibility of a recall being required by FDA if the manufacturer has misjudged the categorization of the supplement. This uncertainty has resulted in blood establishments often pursuing an unnecessarily conservative approach to reporting certain types of changes and, consequently, implementing new technologies slower than necessary. **In order to help blood establishments implement process improvements more efficiently, we request that the proposed rule be revised to include examples of circumstances under which a cease distribution and subsequent recall would likely be ordered and those under which it would not.**

SECTION 601.12(d)(2)(vii)

This section states that additions, deletions, or *revisions* to alternative analytical procedures *that provide the same or increased assurance of the identify, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application* be included in the annual report. Blood establishments currently are permitted to utilize 21 CFR 640.120 to obtain approval for alternate procedures. Since FDA will already be aware of this change on the date they have granted the approval, such change should not need to be included in blood industry annual reports. **In keeping with the paperwork reduction principles of FDAMA, we request that this section be revised so reporting of changes already approved under 640.120 requests is not required in an annual report.**

SECTION 601.12(d)(3)(iii)

This added section will require blood establishments to submit a statement that the effects of the change have been validated. Although minor, this is an additional increase in the documentation and reporting burden for the blood industry. **Because blood establishments are already required to keep validation documentation on file, and blood establishments are inspected on a regular basis, we request that the requirement to submit such a statement be deleted for blood establishments.**

SECTION 601.12 (f)(2)(i)(E)

FDA is proposing to include this new section on labeling, which covers *any other labeling changes specifically requested by FDA,* to enable the agency to allow for labeling changes that normally require prior approval to be submitted in a changes being effected supplement when FDA specifically requests the change. We appreciate this effort to reduce unnecessary reporting and encourage the agency to continue its efforts in this regard. However, industry wide labeling changes could be categorized as annual report for blood establishments since uniform labeling requirements already exist, and the blood establishment would simply be reporting that they have adopted the change. In addition, FDA already permits reporting of changes to procedures initiated at the request of FDA to be reported in an annual report. **We request that for blood establishments, FDA required labeling changes be reported to FDA in an annual report.**

Once again, CFBS appreciates the opportunity to comment on FDA's proposed rule, Supplements and Other Changes to an Approved Application. Should you have any questions concerning our comments, please feel free to contact Kay R. Gregory, MS, MT(ASCP)SBB, AABB Director, Regulatory Affairs at (301) 215-6522 or by e-mail to kayg@CFBS.org.

Sincerely,

Roger Brinser

Roger Brinser
Chair, Coalition For Blood Safety